Joint NDAC/DODAC Advisory Committee Meeting
March 24, 2005

Executive Summary

The focus of this advisory committee is to discuss the safety considerations related to the switch of dermatologic corticosteroids from prescription to over-the-counter (OTC) use. The discussion will center on pre-switch assessments of safety regarding both local and systemic adverse events.

BACKGROUND

The only dermatologic corticosteroid currently marketed for OTC use is hydrocortisone (hydrocortisone acetate). Hydrocortisone was originally introduced into the market as a prescription drug in 1952. FDA received a petition in 1956 to switch hydrocortisone from prescription to OTC status. We initially rejected this petition for two reasons: (1) consumers' ability to safely self-medicate had not been demonstrated and (2) more testing was needed on percutaneous absorption. However, we later reconsidered and allowed 0.25% to 0.5% hydrocortisone to be marketed OTC as an anti-pruritic in 1979 under an OTC drug monograph for external analgesic products (see Tab 2). This was based on consideration of several studies evaluating potential systemic effects of dermatologically applied hydrocortisone and concluding that the clinical data did not preclude topical hydrocortisone from being safely marketed. For example, one study indicated that hydrocortisone, applied topically for prolonged periods of time, did not cause HPA axis suppression (evaluated by insulin stress testing) in patients with chronic skin disease (*i.e.*, eczema or psoriasis) (see Tab 5). However, this study was not conducted using current standards for HPA axis suppression (*i.e.*, cosyntropin/cortrosyn stimulation test). In 1990, we amended the external analgesic monograph to allow 0.25% to 1.0% hydrocortisone use as an anti-pruritic (see Tab 4). Currently, under the external analgesic monograph, any manufacturer currently can market a product containing 0.25% to 1.0% hydrocortisone as an anti-pruritic without pre-approval by FDA.

Because pre-approval is not required for OTC products marketed under the external analgesic monograph, FDA requires that such products must contain specific labeling. OTC products containing hydrocortisone must be labeled with the following indication: "for the temporary relief of itching associated with minor skin irritations, inflammation, and rashes." Optionally, this may be followed by: "due to eczema, psoriasis, seborrheic dermatitis, insect bites, poison ivy, poison oak, poison sumac, soaps, detergents, cosmetics, jewelry, and/or external genital, feminine, and anal itching."

Additional required labeling includes a warning that consumers using OTC external analgesic products containing hydrocortisone must "stop use and ask a doctor if conditions worsen, last longer than seven days, or clear up and occur again within a few days." Finally, directions on a hydrocortisone-containing OTC product must specify that adults and children over 2 years of age are not to use the product more than 3 to 4 times daily and the product is not to be used on children under 2 years of age.

Recently, we have met with sponsors requesting Rx-to-OTC switches for dermatologic corticosteroids that are more potent than hydrocortisone. We are convening this advisory committee to seek guidance on potential safety data necessary for the switch of more potent corticosteroids. These data could include, but are not limited to, HPA axis suppression, growth suppression, and local adverse events for a potential OTC dermatologic corticosteroid.

Potential effects from glucocorticoids (including topical)

HPA axis suppression

The hypothalamic-pituitary-adrenal axis is sensitive to exogenous topical or systemic corticosteroid administration. Even relatively short-term therapy (e.g. 4 weeks) with exogenous corticosteroids can suppress the HPA axis to the point where normal stress-related increase in cortisol levels fails to occur. Failure to increase cortisol secretion in these situations can result in acute adrenal insufficiency, which in some circumstances can be life threatening (see Tab 7).

HPA axis suppression from use of topical corticosteroids has been demonstrated in studies using $ACTH_{1-24}$ (cosyntropin) stimulation testing. Increased risk for HPA axis suppression may result from prolonged use or application to an increased body surface area leading to greater systemic exposure. The risk for HPA axis suppression may be greater in pediatric patients due to increased body surface area to mass ratio.

The recommended testing for HPA axis suppression with the use of corticosteroids is the cosyntropin stimulation test. The currently used criterion for suppression is a serum or plasma cortisol level post-cosyntropin stimulation of less than or equal to 18 micrograms per deciliter 30 minutes after stimulation. The currently recommended dose of cosyntropin for these tests (as discussed in the label for cosyntropin) is 250 micrograms or 125 micrograms for pediatric patients age 2 years or younger, administered as an intravenous bolus in the morning.

Inclusion of sufficient numbers of pediatric patients in any assessment of HPA axis suppression is recommended. For safety reasons, we recommend the more potent topical corticosteroids be tested sequentially starting with adults, followed by progressively younger subsets of pediatric patients.

A lack of patients suppressed in a given HPA axis study only assures, at a given level of confidence, that such suppression is unlikely for the general population. The greater the number of patients enrolled in a study resulting in no findings of HPA axis suppression, the greater level of confidence that a safety concern to this regard is unlikely (see Tab 8). The level of confidence and the rate of HPA axis suppression considered safe for OTC dermatologic corticosteroids will be addressed by the Committee. The Committee should also consider whether labeling that limits duration of use (e.g. to seven days) can effectively reduce safety concerns about HPA axis suppression effects.

Growth suppression

Long-term systemic exposure to corticosteroids has been studied with regard to growth suppression. It is plausible that topical administration of exogenous corticosteroids may result in growth suppression as a result of systemic exposure. However, growth studies may be difficult to perform with topical corticosteroids used for dermatologic conditions. Continuous corticosteroid use at the same potency and dose throughout the long study period required for growth studies is not likely for dermatologic conditions in the pediatric age group.

Glucose intolerance

Corticosteroids have the potential to cause glucose intolerance, especially in more sensitive patients (e.g. diabetics). This effect was explored for 1.0% hydrocortisone as discussed in the OTC drug monograph amendment (see Tab 4). Studies reviewed at that time disclosed "no significant systemic effect" (i.e., changes in blood glucose levels).

Osteoporosis

Long-term systemic exposure to corticosteroids has been studied with regard to potential for bone loss (e.g., osteoporosis). It would be difficult to establish that topical corticosteroid use would result in bone loss (see Growth suppression above).

Sodium retention

Corticosteroids have the potential to cause sodium retention (i.e., mineralocorticoid effect). Of the corticosteroids used topically, hydrocortisone has relatively greater mineralocorticoid potency than triamcinolone or betamethasone. The effect may be minimal with topical administration due to relatively low acute systemic exposure combined with much lower mineralocorticoid potency compared to glucocorticoid potency.

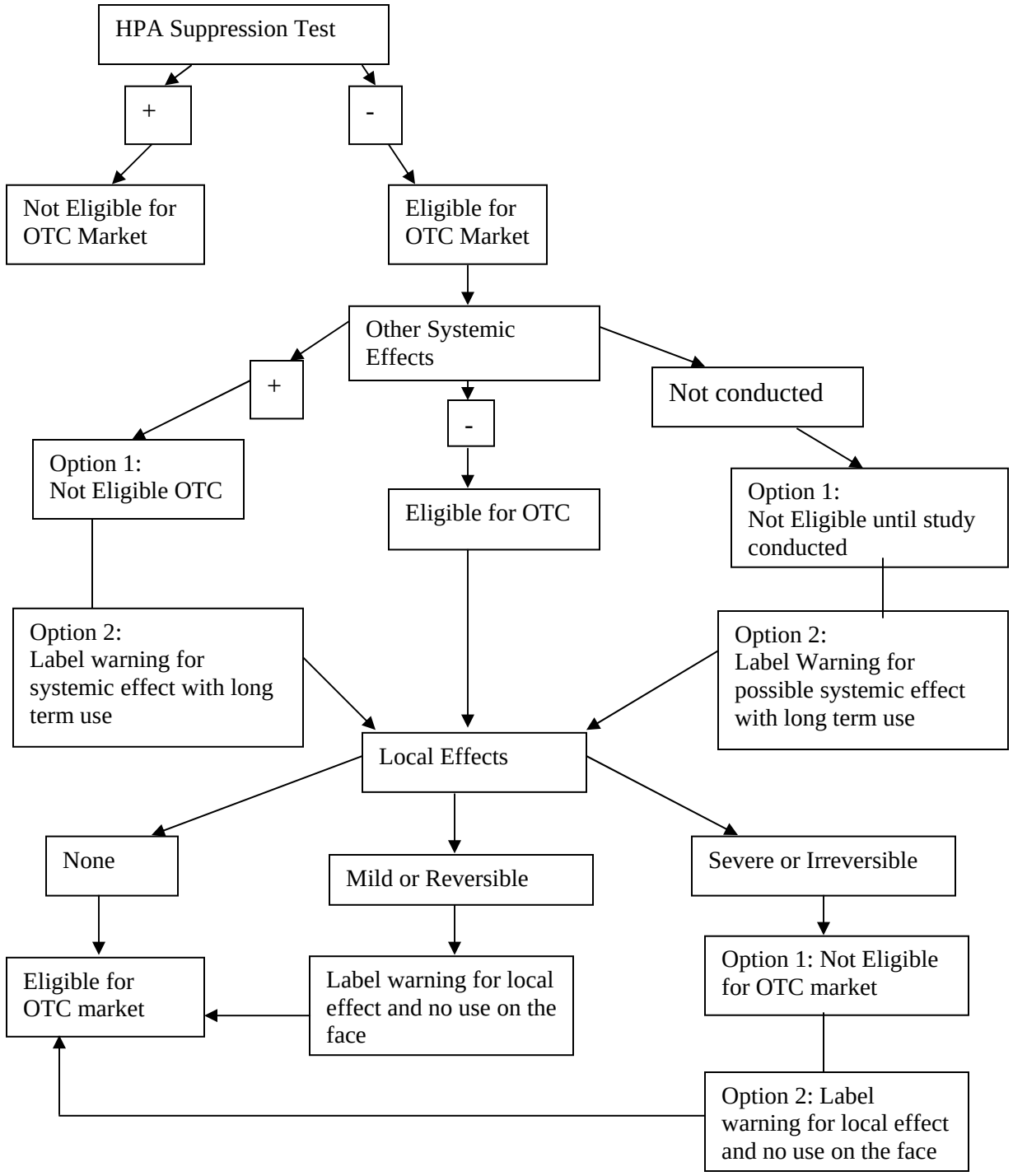
Local skin adverse effects

Additional safety considerations for topical corticosteroids include local safety concerns, such as cutaneous atrophy, striae, erythema of the face, telangiectasia, hypopigmentation and retarded wound healing. The unwanted local application site effects of topical steroids may be related to their potencies and the duration and site of application. In addition, these effects may be worse with use under occlusion.

SAFETY DATABASE

When considering the safety of these products for OTC use, a key consideration is the safety of the product when used by the lay consumer without an learned intermediary. Post-marketing adverse event reports related to HPA axis suppression are rare with topical corticosteroid use. However, consumers not associate the signs and symptoms of HPA axis suppression with a topical drug product. Thus, we are considering whether HPA axis suppression should be the primary safety concern for OTC marketing. Additional systemic effects, such as mineralocorticoid effects, glucose intolerance, growth suppression in children, and bone density changes in adults are also a concern, but measuring the effect of topical corticosteroids on these parameters is difficult at best. Local skin effects may be greatly minimized by limiting the potency of corticosteroids available, the amount available in unit packaging, and the duration of therapy through labeling.

A regulatory decision tree has been devised for the Committee to review and to stimulate discussion. This decision tree lists options based on the results of HPA axis suppression testing, growth suppression testing, and local effects. The decision tree places a hierarchy on the clinical importance of the various side effects (HPA axis suppression followed by other systemic effects, in turn followed by local effects):



Draft Discussion Questions for the Advisory Committee:

1. Does the potential for suppression of the HPA axis with the use of a dermatologic corticosteroid preclude OTC marketing?

2. The number of subjects evaluated provides for the confidence in ruling out HPA axis suppression at a desired upper limit. With a 95% confidence limit, what is the greatest rate of HPA axis suppression to be ruled out (e.g., 0.5%, 1%, 5%, or 10%)?

3. Beyond HPA axis suppression, are there other safety concerns that would not permit OTC marketing of topical corticosteroid?

4. Would labeling for the systemic effects other than HPA axis suppression be an acceptable regulatory path in lieu of asking for growth suppression studies (or other tests of systemic effect, e.g. glucose intolerance testing, tests for bone density)?

5. With regard to dermatologic local effects, at what level of severity do risks outweigh the benefits of topical corticosteroid use in OTC setting?

Appendix

TAB 1 From Valencia, E.C. and F.A. Kerdel, "Topical Glucocorticoids," in Freedberg, I.M., A.Z Eisen, K. Wolff, K.F. Austen, L.A. Goldsmith, and S.I. Katz, eds., "Fitzpatrick's Dermatology in General Medicine, Volume II," p. 2325, 2003.

Potency Ranking Of Some Commonly Used Brand-Name Glucocorticoids,

TAB 2 Recommendations Regarding the Safety and Effectiveness of Hydrocortisone, Advance Notice of Proposed Rulemaking (44 FR 69768 at 69813 - 69824) 1979.

The Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products (the Topical Analgesics Panel) met from 1972 to 1978 to evaluate the safety and effectiveness of active ingredients in OTC external analgesic drug products. One of the active ingredients reviewed was hydrocortisone (hydrocortisone acetate). Attached is the Topical Analgesics Panel's review of hydrocortisone (published in volume 44 of the Federal Register, December 1979). The panel recommended that hydrocortisone be generally recognized as safe and effective as an OTC antipruritic active ingredient.

TAB 3 FDA Concurrence with the Recommendation of the Topical Analgesics Panel, Tentative Final Monograph (48 FR 5852 at 5865 - 5869), 1983.

FDA agreed with the Topical Analgesics (Advisory Review) Panel recommendation that hydrocortisone and hydrocortisone acetate be considered safe and effective as OTC antipruritic active ingredients. Both the panel and FDA classified hydrocortisone and hydrocortisone acetate as Category I (safe and effective) active ingredients. Attached is an excerpt from volume 48 of the Federal Register which summarizes FDA's position with respect to the Topical Analgesics Panel's recommendations. The excerpt includes Part 348 of the Code of Federal Regulations listing hydrocortisone and hydrocortisone acetate, 0.25 to 0.5 percent, as active ingredients (21 CFR 348.10(d)(1) and (d)(2)) and defining appropriate labeling (21 CFR 348.50).

TAB 4 FDA Recognition that Hydrocortisone is Safe and Effective as an OTC Antipruritic Active Ingredient at Concentrations up to 1.0 Percent, Amendment of Tentative Final Monograph (55 FR 6932), 1990.

In response to a citizen petition, FDA agreed that hydrocortisone can be considered safe an effective as an OTC antipruritic active ingredient at concentrations greater than 0.5 percent up to a maximum of 1.0 percent. FDA's reasoning and conclusions were published in volume

55 of the Federal Register. This publication dealt exclusively with the safety and effectiveness of hydrocortisone and is attached in its entirety.

TAB 5 Munro, D.D. and D.C. Clift, "Pituitary adrenal function after prolonged use of topical corticosteroids," British Journal of Dermatology, 88:381-385, 1973.

Clinical study referred to by Advisory Review Panel in considering the safety of hydrocortisone as an antipruritic. 40 patients with chronic skin disease (eczema, psoriasis) were treated with topically applied corticosteroids including 1.0 percent hydrocortisone for periods ranging from less than 10 to over 100 months. Hypothalamic-pituitary-adrenal axis function was measured by evaluating response to insulin stress.

TAB 6 Munro, D.D.**,** "The effect of percutaneously absorbed steroids on hypothalamic –pituitary-adrenal function after intensive use in in-patients" British Journel of Dermatology 94:67-76:1976

This is a study in HPA axis suppression in adults and children comparing betamethasone valerate, 0.1% ointment and hydrocortisone acetate, 1% ointment.

TAB 7 Cooper, M.S. and P.M. Stewart, "Corticosteroid Insufficiency In Acutely Ill Patients," New England Journal of Medicine, :727-734, 2003.

Review article describing activity of the hypothalamic-pituitary-adrenal (HPA) axis operating normally and when suppressed (as may occur in acute illness).

TAB 8 Hanley, J.A., and A. Lippman-Hand, "If Nothing Goes Wrong, Is Everything All Right? Interpreting Zero Numerators," Journal of American Medical Association, 249:1743-1745, 1983.

TAB 9 Ellison ,J.A., L. Patel, D.W. Ray, and P.E. Clayton, "Hypothalamic-Pituitary-Adrenal Function and Glucocorticoid Sensitivity in Atopic Dermatitis," Pediatrics 105:794-799, 2000.

Study of hypothalamic-pituitary-adrenal axis function in 35 pediatric patients with atopic dermatitis. Seven patients were treated with mildly potent dermatologic corticosteroids; 17 patients were treated with moderately potent corticosteroids, and 4 were treated with potent/very potent corticosteroids.

TAB 10 Seth, A. and A. Aggarwal, "Monitoring Adverse Reactions to Steroid Therapy in Children," Indian Pediatrics 41:349-357, 2004.

Review article describing the adverse consequences of long term steroid use in children.

TAB 11 Dorin, R.I., C.R. Qualls, and L.M. Crape, "Diagnosis of Adrenal Insufficiency," Annals of Internal Medicine 139:194-206, 2003.

A discussion about cosyntropin stimulation testing for evaluation of adrenal insufficiency

TAB 12 Table: Relative Glucocorticoid And Mineralocorticoid Potency Of Natural Corticosteroids And Some Synthetic Analogs In Clinical Use, from: Berne, R.M. and M.N. Levy (eds.), "Physiology," The C.V. Mosby Company, St. Louis, p. 1046, 1983.

This table shows the relative glucocorticoid and mineralocorticoid potencies of some commonly used corticosteroids.

TAB 13 Table: Relative Potencies and Equivalent Doses of Representative Corticosteroids, from: Hardman, J.G., A.G. Gilman, and L.E. Limbird (eds.), Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th ed., McGraw-Hill, New York, p. 1466, 1996.

This table shows that anti-inflammatory and sodium retention potencies do not necessarily correlate for different commonly used corticosteroids.

TAB 14 Abstracts of case studies - long term treatment with topical corticosteroids

TAB 15 Picado, C. and M. Luengo, "Corticosteroid-Induced Bone Loss. Prevention and Management," Drug Safety 15:347-359, 1996.

A review article discussing osteoporosis as an adverse effect of long term treatment with corticosteroids.